

A new approach for molecular docking into homology modeled structures

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Docking into homology modeled structures is very often not a straightforward task. The two major reasons for this are the limited accuracy especially of the side chain positions in protein structures obtained by homology modeling and the dependency of the structural details on the template structures used. Thus often homology modeled structures cannot be used directly for docking purposes. An additional refinement and validation of these structures is necessary first. We present a new refinement strategy and program, *SiteOpt*, for a ligand dependent refinement of homology modeled structures and discuss the influence of the templates used and the improvements gained through our structure refinement.

We chose the cytochrome P450 CYP11B2 as our major test target. CYP11B2 catalyses the final steps of mineralocorticoid (aldosterone) production. High aldosterone levels are responsible for various cardiovascular diseases. Due to the difficulty of resolving membrane bound proteins, there is no experimental structure available for CYP11B2. However, there is an intense ongoing effort to develop homology models of mammalian cytochrome P450s. The quality of these models is strongly dependent on the templates used[1]. For high quality models the template structures should belong to a closely related species and should be similar in function[1].

In our case there was no experimental structure of a mammalian cytochrome P450 available with a closely related function, thus we used the recently resolved human cytochrome CYP2C9 structure (PDB code: 1r9o) as template[2]. We built 3D structural models for CYP11B2. Afterwards we performed an inhibitor based refinement of the protein binding pocket using the *SiteOpt* program. The refinement procedure involved optimization, simulated annealing, and docking steps using a modified potential. We compared the refined model with the original homology model and a previously built structural model for CYP11B2[3], and evaluated it by docking known inhibitors and non-inhibitors into the different models using the FlexX-Pharm docking software[4, 5].

References

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